Guidance for Industry

Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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I. INTRODUCTION

The purpose of this guidance is to assist sponsors and investigators in the clinical development of drugs for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP), which are typically caused by methicillin-resistant *Staphylococcus aureus* (MRSA), Gram-negative Enterobacteriaceae such as *Klebsiella pneumoniae*, or Gram-negative non-Enterobacteriaceae such as *Pseudomonas aeruginosa* and *Acinetobacter* species. Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for treatment of HABP and VABP.[2] This draft guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective and Ophthalmology Drug Products and the Division of Special Pathogen and Transplant Drug Products, pharmaceutical sponsors, the academic community, and the public.[3]

This guidance revises and replaces the draft guidance for industry *Nosocomial Pneumonia — Developing Antimicrobial Drugs for Treatment* published in 1998. It also supersedes, with regard to the development of drugs to treat HABP/VABP, more general guidance issued many years ago (i.e., *Clinical Evaluation of Anti-Infective Drugs (Systemic)* and *Clinical Development*

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[1] This guidance has been prepared by the Office of Antimicrobial Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the divisions to discuss specific issues that arise during the development of their drug product.

and Labeling of Anti-Infective Drug Products,[4] as well as the joint FDA/Infectious Disease Society of America's *General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products*.)[5]

For the purpose of this guidance, we assume that a majority of hospitalized patients will receive initial treatment with intravenous (IV) antibacterial drugs. However, this does not preclude the enrollment of hospitalized patients in oral drug trials of HABP/VABP.

This guidance does not address the development of drugs for other purposes or populations, such as treatment of community-acquired bacterial pneumonia (CABP), viral infections, or atypical bacterial pathogens (e.g., *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*). This guidance does not address pneumonia that occurs in patients living in chronic health care facilities, because bacterial etiologies may differ from HABP/VABP. This guidance does not address the development of aerosolized antimicrobial drugs.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[6]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

HABP and VABP by definition occur in hospitalized patients. A hospital stay of 48 hours or more will place patients at risk for colonization and potential infection with a variety of Gram-positive and Gram-negative facultative bacteria. Examples of etiologic pathogens of HABP/VABP include Gram-positive bacteria such as MRSA, Gram-negative Enterobacteriaceae such as *K. pneumoniae*, and Gram-negative non-Enterobacteriaceae such as *P. aeruginosa* and *Acinetobacter* species. These bacteria are often resistant to multiple antibacterial drugs, which is an increasing concern. It is also recognized that HABP/VABP may be polymicrobial.

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[4] See the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] Beam, TR, DN Gilbert, and CM Kunin, 1992, General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, Infectious Disease Society of America and the Food and Drug Administration, Clin Infect Dis, Nov 15 (Suppl 1): S5-S32.

[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

A synonym for HABP and VABP is *nosocomial pneumonia*. Since the FDA published a draft guidance on the development of antimicrobial drugs for the treatment of nosocomial pneumonia in 1998, there have been public discussions regarding the design of clinical trials to study HABP and VABP, including a workshop on March 31 and April 1, 2009, co-sponsored by the FDA and professional societies.[7] These discussions focused on clinical trial designs for HABP and VABP and other important issues such as the following:

- Noninferiority versus superiority trial designs
- Justification of an appropriate noninferiority margin
- Classification of the severity of illness
- Enrollment criteria
- Application of appropriate diagnostic criteria
- Use of appropriate definitions of clinical outcomes
- Timing of outcome assessments
- Use of prior antimicrobial drugs
- Use of concomitant antimicrobial drugs
- Differences and similarities between HABP and VABP

These discussions and issues have been incorporated into this draft guidance in the appropriate sections below.

III. DEVELOPMENT PROGRAM

We encourage sponsors to contact the appropriate review division to discuss specific issues that arise during the development of their drug.

A. General Considerations

1. Definition of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

HABP is defined as an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms such as fever or hypothermia, chills, rigors, cough, purulent sputum production, chest pain, or dyspnea, accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient hospitalized for more than 48 hours or developing within 7 days after discharge from a hospital.[8]

[7] Transcripts of the March 31 and April 1, 2009, workshop, *Clinical Trial Design for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia*, can be found at http://www.fda.gov/Drugs/NewsEvents/ucm169877.htm.

[8] Oral and nasotracheal bacterial flora may not return to normal flora within 4 to 6 weeks or longer after hospitalization and some treatment guidelines describe “hospital-acquired pneumonia” as occurring within 3 months after hospital discharge. However, the goal of this guidance is to provide a definition of HABP that enriches clinical trial populations with bacterial pathogens most commonly identified in HABP and VABP, and we are defining HABP as occurring within 7 days after hospital discharge. Therefore, the definition of HABP in this guidance may differ in some respects from treatment guidelines or other clinical decision tools for consideration of antibacterial therapy.

VABP is defined as an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms such as fever or hypothermia, chills, rigors, purulent respiratory secretions, and increased oxygen requirements accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient receiving mechanical ventilation via an endotracheal (or nasotracheal) tube for a minimum of 48 hours. Although some epidemiological studies have shown that patients with VABP may be more likely to have bacterial pathogens resistant to multiple antibacterial drugs, these pathogens have also been observed in HABP and therefore the guidance considers these two clinical disease entities together, referred to as HABP/VABP.

The more general term *health care-associated pneumonia*, or pneumonia among persons residing in chronic care facilities such as nursing homes, is not considered to be HABP as defined in this guidance because the bacterial pathogens in these patients with the broader category of health care-associated pneumonia are, in general, less likely to be similar to bacterial pathogens in patients with HABP/VABP.[9,10]

2. Nonclinical Development Considerations

New antibacterial drugs being studied for HABP/VABP should have nonclinical data documenting activity against commonly implicated pathogens for HABP/VABP (e.g., MRSA or Gram-negative Enterobacteriaceae such as *K. pneumoniae* and non-Enterobacteriaceae such as *P. aeruginosa* or *Acinetobacter* species).

Animal models of acute pneumonia have been developed and may contribute to evaluating antimicrobial activity. Animal studies are not a substitute for the clinical trials in patients with HABP/VABP that must be conducted to evaluate safety and efficacy of the drug.[11]

3. Drug Development Population

The intended clinical trial population is patients with HABP/VABP. In addition to having the clinical syndrome of bacterial pneumonia described in section III.A.1., Definition of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia, the primary analysis populations should consist of patients with bacteriological confirmation of the etiologic agent. The clinical disease spectrum of HABP/VABP in pediatric patients may be different from adults and, therefore, sponsors should discuss pediatric development with the FDA early in clinical development (e.g., the potential extrapolation of adult efficacy data to children with HABP/VABP and the appropriate pharmacokinetic and safety data in children).

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[9] The American Thoracic Society and the Infectious Disease Society of America, 2005, Guidelines for the Management of Adults With Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia, Am J Respir Crit Care Med, 171:388-416.

[10] For example, approximately 25 percent of VABP was caused by *P. aeruginosa* (the most common gram-negative pathogen causing HABP/VABP); some epidemiological information demonstrated that only 4 percent to 14 percent of health care-associated pneumonia was caused by *P. aeruginosa*.

[11] See 21 CFR 314.600.

4. Dose Selection

To choose the dose or doses to be evaluated in phase 3 clinical trials, sponsors should integrate the findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics, pharmacodynamics, safety and tolerability information from phase 1 clinical trials, and safety and efficacy information from phase 2 dose-ranging clinical trials. Studies assessing drug penetration at the site of action (e.g., epithelial lining fluid) can be helpful in defining doses that achieve concentrations sufficient to exert an antimicrobial effect within the lungs. In addition, the pharmacokinetics of the drug in specific populations (e.g., geriatric patients, patients with renal and hepatic impairment) should be evaluated before initiation of phase 3 trials to determine whether dose adjustments are necessary (see section III.C., Other Considerations, for pharmacokinetic (PK) issues). This evaluation may help avoid the exclusion of such patients from phase 3 clinical trials.

5. Efficacy Considerations

Either noninferiority or superiority trial designs can be used to support this indication. HABP/VABP clinical trials should be designed to demonstrate a treatment effect of antibacterial therapy on all-cause mortality in patients with HABP/VABP caused by bacterial pathogens (such as MRSA or Gram-negative Enterobacteriaceae such as *K. pneumoniae* and non-Enterobacteriaceae such as *P. aeruginosa* or *Acinetobacter* species). The primary analysis population should be patients with a microbiologically confirmed bacterial etiology for HABP/VABP (see section III.B.12.a., Analysis populations). If sponsors wish to include additional organisms in clinical trials for this indication, they should provide data sufficient to substantiate the clinical relevance of the particular organism as a pathogen in HABP/VABP.

The number of clinical trials needed to support an HABP/VABP indication depends on the overall development plan for the drug under consideration. If the development plan for the drug has HABP/VABP as the sole indication, then two adequate and well-controlled trials should support evidence of safety and effectiveness. Because similar drug-resistant bacteria occur in both HABP and VABP, and confirmation of a bacterial pathogen may be more likely to occur in patients with VABP, two clinical trials that demonstrate safety and efficacy in patients with VABP can provide support for an indication that encompasses both HABP and VABP. One successful trial in HABP and one successful trial in VABP can provide support for an indication that encompasses both HABP and VABP. Two successful trials in HABP can provide support for an indication for HABP only. We recommend that patients with only VABP or only HABP be enrolled in clinical trials. Microbiological diagnosis also permits analysis of treatment response by individual pathogen. If a drug is being developed for other respiratory infections, sponsors should discuss with the FDA whether other trials might lend support to a HABP/VABP indication.

We anticipate that patients will receive an IV formulation for treatment of HABP/VABP. For drugs that have both an IV and oral formulation, and when a switch to the oral formulation is included in the protocol, the appropriate objective criteria that allow for the IV to oral switch should be specified in the protocol and listed on the case report form. Those criteria should be discussed with the FDA before trial initiation. The pharmacokinetics of the oral formulation should have been adequately evaluated to determine an appropriate dosing regimen and to ensure exposure comparable to the intravenous formulation.

Currently, we do not recognize any surrogate markers or clinical endpoints as substitutes for all-cause mortality outcomes in HABP/VABP trials. Sponsors who wish to propose an alternative endpoint for outcomes of HABP/VABP should discuss this with the FDA early in the drug development process.

6. Safety Considerations

The protocol should specify the methods to be used to obtain safety data during the course of the trial. Both adverse event information and safety laboratory data should be collected. All patients should be evaluated for safety at the time of each visit or assessment, regardless of whether the test drug has been discontinued. All adverse events should be followed until resolution, even if time on trial would otherwise have been completed.

A sufficient number of patients, including patients older than 65 years and patients with renal impairment, should be studied at the dose and duration proposed for use to draw appropriate conclusions regarding drug safety. Safety evaluations and assessments should take into consideration the patient populations that are likely to be treated for HABP/VABP. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations may be needed based on the nonclinical and clinical profile of the specific drug under investigation. Longer term assessment of adverse events after discontinuation or completion of the antimicrobial should be considered, depending on the specific drug's potential for long-term or delayed adverse effects.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Design

HABP/VABP trials should be randomized, double-blind, and active-controlled using a noninferiority or superiority design. Trials can include only HABP patients, only VABP patients, or patients with either HABP or VABP. However, we recommend that only HABP or only VABP patients be enrolled in trials (see section III.A.1., Definition of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia).

2. Trial Population

The trial population should include patients with HABP/VABP who are sufficiently ill that an estimate of their probable mortality within a reasonable time frame (e.g., 28 days after initiation of therapy for HABP/VABP) is approximately 20 percent or more. This can be accomplished by enrollment of an older patient population or patients with a threshold clinical severity score that predicts more severe illness or higher rate of mortality. The primary analysis population should include patients with microbiologically confirmed HABP/VABP infections caused by bacteria implicated in HABP/VABP (e.g., MRSA, Gram-negative Enterobacteriaceae such as *K.*

pneumoniae, or Gram-negative non-Enterobacteriaceae such as *P. aeruginosa* and *Acinetobacter* species) to allow assessment of the drug's effectiveness based upon the prespecified noninferiority margin, as described in section III.B.12., Statistical Considerations.

3. Entry Criteria

a. Radiographic, clinical, and microbiologic criteria

The patient should have a clinical picture of a new onset of bacterial pneumonia at a minimum of 48 hours after hospitalization or following 48 hours of mechanical ventilation, or within 7 days of discharge from a hospital, with new or evolving infiltrate(s) on chest radiograph, which is not related to another disease process.

Radiographic criteria.
The chest radiograph should show the presence of ***new*** infiltrate(s) characteristic of bacterial pneumonia. The final full report of the chest radiograph by a qualified medical professional who is not the principal investigator of the trial (e.g., a radiologist or pulmonologist masked to treatment assignment) should be included on the case report form.

Clinical criteria.
Patients should have the following clinical findings that support a diagnosis of HABP/VABP:

- Documented fever, defined as an oral or tympanic temperature greater than or equal to 38 degrees Celsius (100.4 degrees Fahrenheit), or a core temperature greater than or equal to 38.3 degrees Celsius (101 degrees Fahrenheit) or hypothermia, defined as a core body temperature of less than 35 degrees Celsius (95.2 degrees Fahrenheit); axillary temperatures are not recommended

- An elevated total peripheral white blood cell (WBC) count (WBC greater than 10,000/mm); or greater than 15 percent immature neutrophils (bands), regardless of total peripheral WBC count; or leukopenia with total WBC less than 4,500/mm

- New onset of expectorated or suctioned respiratory secretions characterized by purulent appearance indicative of bacterial pneumonia

In addition, patients with **HABP** should have at least one of the following present at enrollment:

- A new onset of cough (or worsening of baseline cough) during 48 or more hours of hospitalization or within 7 days after discharge from a hospital

- Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (e.g., dullness on percussion, bronchial breath sounds, or egophony)

- Dyspnea, tachypnea, or respiratory rate greater than 30/minute, particularly if any or all of these signs or symptoms are progressive in nature

- Hypoxemia (e.g., a partial pressure of oxygen less than 60 mm Hg while the patient is breathing on room air as determined by arterial blood gas or oxygen saturation less than 90 percent while the patient is breathing on room air as determined by pulse oximetry, or worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO2/FiO2), or respiratory failure requiring mechanical ventilation)

In addition, patients with **VABP** should have a Clinical Pulmonary Infection Score of greater than 6,[12] and at least one of the following present at enrollment:

- Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (e.g., dullness on percussion, bronchial breath sounds, or egophony)

- Acute changes made in the ventilator support system to enhance oxygenation, as determined by arterial blood gas, or worsening PaO2/FiO2

We recommend using a clinical severity scoring system for the purposes of defining enrollment criteria to ensure a clinical trial population with a reasonable likelihood of predicting mortality of approximately 20 percent or greater. The protocol should provide the rationale for the use of a particular severity scoring system (e.g., Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III, Sequential Organ Failure Assessment, Multiple Organ Dysfunction Score, or predisposition, insult, response, and organ dysfunction score) and the inclusion criteria should define a minimum score that has a reasonable likelihood of predicting mortality of approximately 20 percent or greater. For example, an inclusion criterion of patients with an APACHE II score of 15 or greater might help to predict a clinical trial population with a mortality rate of 20 percent or greater.

Microbiologic criteria.
Patients with HABP/VABP and a bacterial pathogen isolated from respiratory secretions or blood (e.g., MRSA, Gram-negative Enterobacteriaceae such as *K. pneumoniae*, or Gram-negative non-Enterobacteriaceae such as *P. aeruginosa* and *Acinetobacter* species) should be eligible for inclusion in the primary analysis population depending on the antibacterial activity of the investigational drug. At the time of enrollment before administration of clinical trial antimicrobial therapy, an adequate specimen of respiratory secretions should be obtained in all patients and sent to the laboratory for Gram stain and culture with in vitro antibacterial susceptibility testing performed on appropriate organisms isolated from the specimen. Specimens should be processed according to recognized methods.[13]

Microscopic examination of Gram stained smears should be performed. For expectorated sputum in HABP trials, specimens that have fewer than 10 squamous epithelial cells and more

[12] For example, see Pugin, J, R Auckenthaler, N Mili, et al., 1991, Diagnosis of Ventilator-Associated Pneumonia By Bacteriologic Analysis of Bronchoscopic and Non-Bronchoscopic “Blind” Bronchoalveolar Lavage Fluid, Am Rev Resp Dis, 143:1121-1129; or Singh, N, P Rogers, CW Atwood, MM Wagener, VL Yu, 2000, Short-Course Empiric Antibiotic Therapy for Patients with Pulmonary Infiltrates in the Intensive Care Unit, Am J Respir Crit Care Med, 162: 505-511.

[13] For examples, see the most current editions of the publications from American Society for Microbiology, such as *Manual of Clinical Microbiology* and *Clinical Microbiological Procedures Handbook.*

than 25 polymorphonuclear cells per low power field (100X magnification) should be considered appropriate for inclusion in evaluation of respiratory culture results. Specimens obtained from bronchial brush or endotracheal suction (VABP trials) generally should be appropriate for inclusion in evaluation of respiratory culture results (e.g., fewer than 10 squamous epithelial cells). Ten to 20 fields of the Gram stain smear also should be examined at 1,000X magnification and the morphology of potential pathogens recorded. If the specimen is kept at room temperature, the Gram stain should be performed and the specimen plated for culture within 2 hours from the collection time. Alternatively, these tests can be performed within 24 hours of collection if the specimen is stored at 2 to 8 degrees Celsius before processing.

An appropriate lower respiratory tract specimen can be obtained by any of the following modalities:

- Deep expectoration
- Endotracheal aspiration in intubated patients
- Bronchoscopy with bronchoalveolar lavage or protected-brush sampling

All isolates considered to be possible pathogens should be saved in the event that additional testing of an isolate is needed. For microbiological assessment, the investigator should describe how the sample was obtained, processed, and transported to the laboratory and identify the bacterial isolate(s). The protocol should characterize the microbiological findings based on the type of specimen collection. For example, colony counts of 10^3 colony forming units/ml (CFU/ml) can be considered a threshold for identifying pathologic bacteria from protected brush specimen whereas colony counts of 10^6 CFU/ml can be considered a threshold for identifying pathologic bacteria from an endotracheal tube specimen.

In vitro susceptibility testing should be performed on all isolates to the test drug, the comparator drug, and other antibacterial drugs that may be used to treat HABP/VABP caused by the targeted pathogens (e.g., MRSA, Gram-negative Enterobacteriaceae such as *K. pneumoniae*, or Gram-negative non-Enterobacteriaceae such as *P. aeruginosa* and *Acinetobacter* species). In vitro susceptibility tests should be performed by using standardized methods unless otherwise justified.[14] Sponsors should describe the exact methodology used for susceptibility testing if a standardized method was not used.

The following topics regarding detection of bacterial pathogens should be discussed with the FDA before trial initiation: (1) use of rapid diagnostic tests for bacterial pathogens or for respiratory viral pathogens; and (2) use of biomarkers for detection of patients with bacterial disease.

b. Exclusion criteria

In addition to complying with general exclusion criteria applicable to other trials, sponsors should exclude the following patients from HABP/VABP clinical trials:

[14] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute.

- Patients with known or suspected CABP or viral pneumonia

- Patients with acute exacerbation of chronic bronchitis without evidence of pneumonia

- Patients with tracheobronchitis

- Patients who have received prior antibacterial drugs within the past 30 days with activity against bacterial pathogens that cause HABP/VABP

- Patients with known bronchial obstruction or a history of post-obstructive pneumonia (this does not exclude patients with pneumonia who have underlying chronic obstructive pulmonary disease)

- Patients with primary lung cancer or another malignancy metastatic to the lungs

- Unless the trial is specifically designed for such a patient population, patients with cystic fibrosis, bronchiectasis, HIV/AIDS, known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis

- Patients with a clinical severity score that is associated with a greatly increased probability of survival

4. Randomization, Blinding, and Stratification

Patients should be randomized to treatment groups at enrollment. To the extent possible, the test antibacterial drug and the active-controlled antibacterial drug should be administered in a double-blinded fashion. If there is a compelling reason for single-blind or open-label trial designs, efforts to minimize bias should be discussed with the FDA before trial initiation.

We recommend stratification by age and by the location in the hospital (e.g., patients admitted to a surgical intensive care unit, patients admitted to a medical intensive care unit).

5. Special Populations

The trials should include patients of both sexes and all races. If sponsors wish to include pediatric patients in HABP/VABP clinical trials, they should discuss the development plans with the FDA. Patients with renal or hepatic impairment can be enrolled provided that pharmacokinetics of the drug have been evaluated in these patients and appropriate dosing regimens have been defined (see section III.A.1., Definition of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia).

6. Choice of Comparators

Placebo-controlled trials that do not incorporate antibacterial treatment for HABP/VABP are not appropriate for this indication. The active comparator should be an antibacterial drug at the recommended dosage that is FDA-approved for treatment of "nosocomial pneumonia" or

"HABP/VABP" or is FDA-approved for the treatment of "lower respiratory tract infections" with the appropriate antibacterial spectrum for pathogens encountered in HABP/VABP. Sponsors should discuss with the FDA the choice of the control antibacterial drug if the drug is FDA-approved for "lower respiratory tract infections." Ideally, the comparator drug selected would also be a drug recommended in current treatment guidelines for HABP/VABP.

7. Prior Antibacterial Drug Use

The use of prior antibacterial drugs effective against bacteria that cause HABP/VABP should be avoided in a noninferiority trial because such treatments will reduce the difference between treatment arms and potentially bias conclusions about treatment effects. However, patients who have received prior antibacterial therapy and who are considered clinical failures on that therapy can be enrolled provided objective criteria for treatment failure are prespecified and documented on the case report form. Patients can also be enrolled if they have received prior antibacterial therapy that lacks in vitro activity against bacteria that cause HABP/VABP.

8. Concomitant Antibacterial Drugs

The broad bacterial spectrum and emerging resistance of bacterial pathogens causing HABP/VABP enhances the challenges in the design of clinical trials for this indication. An investigational drug may not fully encompass all bacterial pathogens implicated in HABP/VABP. For example, an investigational drug with in vitro activity against Gram-negative non-Enterobacteriaceae, but no activity against MRSA, can be a drug targeted for development for the treatment of HABP/VABP. Moreover, clinical trial sites may have different patterns of bacterial etiologies responsible for HABP/VABP. The protocol should specify the use of concomitant antibacterial drugs that may be permitted in the trial to provide empirical antibacterial coverage against a wide variety of pathogens, which is often necessary for initial treatment of patients with HABP/VABP before the culture results are available. Furthermore, the use of concomitant antibacterial drugs should be carefully considered in the clinical trial design, because concomitant antibacterial drugs can confound the interpretation of treatment effect in a noninferiority trial.

The investigational drug's in vitro antibacterial activity should be well-characterized, and to the extent possible, the concomitant antibacterial drug should not have antibacterial activity similar to the investigational drug to allow for the assessment of the effect of the investigational antibacterial drug. After the bacterial pathogen has been identified on culture and found on in vitro susceptibility testing to be susceptible to the investigational drug (or to the control drug used in the clinical trial), the protocol should allow for discontinuation of the concomitant antibacterial drugs (that were initially used for empirical antibacterial coverage against a wide variety of pathogens) in the setting of clinical improvement.[15] The course of treatment should be completed as monotherapy with the investigational drug or active-controlled drug, thereby enhancing the possibility of drawing stronger conclusions about an investigational drug's overall

[15] For example, see the recommendations for *de-escalation* of the initial empirical antibacterial drug therapy based on the culture results and in vitro susceptibility testing in the setting of clinical improvement at 48 to 72 hours in The American Thoracic Society, 2005, Guidelines for the Management of Adults With Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia, Am J Respir Crit Care Med, 171:388-416.

treatment effect during a full course of treatment. The use of concomitant antibacterial drugs with similar antibacterial activity to the investigational drug or continuation of the empirical antibacterial coverage during the entire course of treatment will compromise the ability to evaluate the treatment effect of an investigational drug.

9. *Efficacy Endpoints*

The recommended primary endpoint is all-cause mortality within 28 days after randomization.

- Clinical success: patients alive within 28 days after randomization into the clinical trial.

- Clinical failure: patients who have died within 28 days after randomization into the clinical trial.[16]

Generally in HABP/VABP trials, there is no need for primary endpoint adjudication. Secondary endpoints can include outcomes as follows:

- All-cause mortality within 14 days after randomization

- Clinical cure: complete resolution of HABP/VABP signs and symptoms present at enrollment, no new symptoms or complications attributable to HABP/VABP, and alive at 28 days

- Clinical improvement: respiratory rate, heart rate, and temperature recordings at baseline compared to 3 to 5 days of therapy and compared to the end of therapy; time to resolution of HABP/VABP signs and symptoms present at enrollment; or improvement in PaO2/FiO2 over time

- Clinical progression: lack of resolution or worsening of HABP/VABP signs and symptoms present at enrollment and alive at 28 days; administration of rescue antibacterial therapy and alive at 28 days; or administration of antibacterial therapy for another bacterial infection and alive at 28 days

Any endpoint that includes symptom response should use a patient-reported outcome (PRO) measurement for symptom assessment. PRO tools can also be used to assess signs or aspects of functioning that are appropriately assessed by the patient themselves. PRO tools can be self-administered or interviewer-administered, if necessary, using an established script for the interview where the interviewer records only those responses given by the patient. If a PRO tool

[16] Among the studies of HABP/VABP that were evaluated, the exact timing of the follow-up for all-cause mortality was not reported (see Appendix A). The choice of the timing of the endpoint at 28 days after randomization appears to be clinically meaningful and assumes the duration of antibacterial therapy at approximately 2 weeks. Sponsors can discuss with the FDA an alternative timing of the all-cause mortality primary endpoint based on the total duration of administration of trial drugs (e.g., all-cause mortality from the beginning of therapy to 14 days after completion of therapy).

is used, its content validity and other measurement properties should be demonstrated in the population represented in the clinical trial.[17]

Sponsors should be aware that we consider analyses of secondary and additional endpoints to be exploratory, because trials usually are not designed to address the multiplicity questions raised by these analyses. It is possible, however, to identify in the statistical analysis plan the particular analyses and subsets of interest when the trial is successful on its primary endpoint, and, using sequential approaches or multiplicity corrections, reach statistically valid conclusions on secondary endpoints. Analyses of secondary and additional endpoints is often most helpful for identifying areas for study in future trials.

10. Trials in HABP/VABP Patients With Unmet Need

HABP/VABP patients with unmet need (e.g., patients who have or are suspected of having a bacterial pathogen with in vitro susceptibility testing that shows resistance to most antibacterial drugs) may not be appropriate patients for enrollment in a noninferiority trial design (see section III.B.9., Efficacy Endpoints). The noninferiority trial design assumes that the active-controlled drug has a known and reliable treatment effect. Furthermore, antibacterial drug therapy is usually chosen for each individual patient based on the results of in vitro susceptibility testing. Thus, the use of the same control antibacterial drug in a noninferiority trial may not be appropriate for these patients (e.g., if a patient's infectious bacteria are resistant to the control drug).

An active-controlled trial designed to show superiority can be considered in the setting of HABP/VABP caused by bacteria resistant to multiple antibacterial drugs. Such a trial may also enroll patients with a greater degree of comorbid conditions or may be appropriate in the setting where the risk-benefit profile of the drug only supports a more limited use because of its toxicity. Furthermore, important information about a drug's pharmacokinetic/pharmacodynamic (PK/PD) properties can be evaluated in patients with a greater degree of comorbid conditions. The following three conceptual approaches can be considered for superiority clinical trial designs:

1. Patients would be randomized to receive either the investigational drug or antibacterial drug treatment chosen empirically or based on in vitro susceptibility testing when available. The evaluation of efficacy of the investigational drug would be based on a finding of superiority in the group that received the investigational drug versus the group that received the chosen antibacterial drug treatment.

2. All patients would receive antibacterial drug treatment chosen empirically or based on the results of in vitro susceptibility testing when available, and patients would be randomized to receive an investigational drug or matching placebo. The evaluation of efficacy of the investigational drug would be based on a finding of superiority in the group that received the investigational drug plus the chosen antibacterial drug treatment versus the group that received placebo plus the chosen antibacterial drug treatment.

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[17] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

3. Patients would be enrolled in a dose-response trial where two doses for which there is equipoise are compared with the goal of showing superiority in one dose group versus the other dose group.

We encourage sponsors considering superiority clinical trial designs in HABP/VABP patients with unmet need (e.g., HABP/VABP caused by bacteria resistant to multiple antibacterial drugs) to discuss the design with the FDA during protocol development.

11. Trial Procedures and Timing of Assessments

a. Entry visit

At the entry visit, the following information should be captured and recorded on the case report form:

- History and physical examination
- Prior and concomitant drugs
- Baseline clinical signs and symptoms including vital signs
- Chest x-ray or other radiographic imaging of the chest
- Clinical severity score(s)
- Microbiologic specimens: Adequate respiratory specimens as determined by Gram stain, culture of an appropriate respiratory specimen, and blood cultures (using aseptic techniques, aerobic and anaerobic blood cultures obtained from two separate venipuncture sites before administration of antibacterial therapy)
- Laboratory tests as appropriate
- Ventilator settings as appropriate

b. On-therapy visit at days 2 to 4 after enrollment

Patients should be evaluated early in the course of treatment to assess for clinical failure, where rescue antibacterial drug therapy is appropriate, or clinical improvement. This visit should capture clinical observations such as vital signs, physical examination findings, laboratory test results, changes in ventilator settings, supplemental oxygen requirements, microbiology results, or chest x-ray findings. The de-escalation of antibacterial drug therapy should be documented at this visit, as appropriate.

c. Other on-therapy visits

It is important that investigators distinguish between patients who are worsening or not improving (i.e., where antibacterial rescue therapy is appropriate) from patients who are slow to improve but may still remain on assigned therapy and thereby achieve clinical success. Specific objective criteria to initiate rescue therapy should be included in the protocol and should be documented as a study visit, including the collection of a specimen for microbiology assessments (see section III.B.3.a., Radiographic, clinical, and microbiologic criteria).

d. End-of-therapy visit

Patients should be evaluated clinically at the end of the prescribed therapy. Laboratory assessments for safety should be performed at this visit. If the trial drug needs to be continued beyond the protocol-specified duration, objective criteria for extending the therapy should be prespecified in the protocol. Patients without clinical improvement or with progression of signs and symptoms should be considered as having clinical progression and alternative antibacterial rescue therapy should be provided.

e. Day 28 visit

Patients should be assessed in the hospital, in the clinic, by telephone, or by other interactive technology at day 28 for documentation of the all-cause mortality primary endpoint. Although the attribution of the cause of death by the investigator or sponsor may be informative for exploratory endpoints, the primary endpoint is all-cause mortality regardless of the cause of death.

12. Statistical Considerations

The trial's primary and secondary hypotheses and the analysis methods should be prespecified in the protocol and in the statistical analysis plan, and should be finalized before trial initiation. The primary endpoint analysis should be a comparison of all-cause mortality at 28 days after randomization in the clinical trial between test and active-controlled treatment groups. We recommend that the trials be adequately powered to compare all-cause mortality rates between treatment groups. If sponsors choose to test multiple primary or secondary hypotheses, they should address issues related to the potential inflation of false-positive results and control of overall type I error rate caused by multiple comparisons.[18]

a. Analysis populations

The following definitions apply to various analysis populations in HABP/VABP clinical trials:

- Intent-to-treat (ITT) population — All patients who were randomized.

[18] These issues should be discussed with the FDA during protocol development, and if any subsequent changes are considered, they should be discussed with the FDA before incorporation into the statistical analysis plan. See ICH E9 and ICH E10.

- The microbiological intent-to-treat population (MITT population) — All randomized patients who have a baseline bacterial pathogen that causes HABP/VABP against which the investigational drug has antibacterial activity. This includes bacterial pathogens associated with HABP/VABP identified in blood or appropriate sputum specimen (e.g., MRSA, Gram-negative Enterobacteriaceae such as *K. pneumoniae*, or Gram-negative non-Enterobacteriaceae such as *P. aeruginosa* and *Acinetobacter* species). Patients should not be excluded from this population based upon events that occur post-randomization (e.g., loss to follow-up).[19]

- Clinically evaluable or per-protocol populations — Patients who meet the definition for the ITT population and who follow important components of the trial as specified in the protocol.

- Microbiologically evaluable populations — Patients who meet the definition for the MITT population and who follow important components of the trial as specified in the protocol.

- Safety population — All patients who received at least one dose of drug during the trial.

The MITT population should be considered the primary analysis population. Consistency of the results should be evaluated in all populations and any inconsistencies in the results of these analyses should be explored and explanations should be provided in the complete study report.

b. Noninferiority margins

A noninferiority clinical trial design with a prespecified noninferiority margin can be used in the evaluation of a test antibacterial drug for HABP/VABP. The noninferiority margin can be justified based on historical evidence of the sensitivity to drug effect (HESDE) of antibacterial therapy on all-cause mortality in patients with HABP/VABP. Based on a recent review of historical evidence of treatment effects and with an estimate of all-cause mortality in the control group of approximately 20 percent or greater, an M1 is conservatively estimated at 20 percent and a noninferiority margin of 10 percent is recommended to preserve the treatment effect on all-cause mortality evaluated 28 days after randomization.[20]

If the 28-day all-cause mortality rate in the active-controlled group is lower than approximately 20 percent, an approach using the odds ratio metric should be used as the measure for assessing treatment effects. The constancy assumption may not be valid for all-cause mortality rates lower than approximately 20 percent in the control group in a noninferiority trial (see Appendix A); sponsors considering using the odds ratio should discuss their plans with the FDA when their

[19] The attribution of efficacy to an investigational drug would be compromised if a bacterial pathogen has in vitro susceptibility to both the investigational drug and a concomitant drug used for initial empirical antibacterial coverage. Sponsors should address this issue in the protocol, for example, by choosing concomitant antibacterial drugs that do not have overlapping antibacterial activity with an investigational drug, or by excluding patients from the MITT population with baseline pathogens susceptible to both the investigational drug and a concomitant drug.

[20] See Appendix A and Sorbello, A, S Komo, T Valappil, 2010, Noninferiority Margin for Clinical Trials of Antibacterial Drugs for Nosocomial Pneumonia, Drug Inf J, 44(2):165-176.

protocol is being developed.[21] Sponsors should justify the noninferiority margin for the proposed trial design and patients enrolled. For clinical trials with observed active control mortality rate of less than 20 percent, a fixed noninferiority margin of 1.67 based on an odds ratio metric should be used. When the trial is completed, the applicability of the HESDE to the actual patient population enrolled in the trial should be assessed in the final clinical trial report.

c. Sample size

The appropriate sample size for a clinical trial should be based upon the number of patients needed to answer the prespecified hypothesis posed by the trial. The sample size is influenced by several factors, including the prespecified type I and type II error rates, estimate of the control mortality rate, the noninferiority margin, or the magnitude by which the trial drug is expected to be superior (for a superiority trial). The appropriate sample size should be estimated using a two-sided α=0.05.

d. Missing data

There is no optimal way to deal with missing data from clinical trials. Sponsors should make every attempt to limit loss of patients from the trial. Analyses that exclude patients are subgroup analyses, and patients who do not complete the trial may differ substantially from patients who remain in the trial in both measured and unmeasured ways. The method of how missing data will be handled should be specified in the protocol. Interpretation of trial results may be affected if there are missing data. Missing data should be minimal in clinical trials using all-cause mortality as a primary endpoint.

e. Interim analyses and data monitoring committee

If interim effectiveness analyses for success or futility will be performed, they should be prespecified in the protocol and in the analysis plan along with a justification. Details on the operating procedures also should be provided before trial initiation. The purpose of the interim analysis should be stated along with the appropriate statistical adjustment to control the overall type I error rate. It is important that an appropriate firewall be in place to guarantee that the interim analysis will not affect trial conduct and thereby compromise trial results. This can be accomplished by creating an independent data monitoring committee (DMC) that monitors the protocol with prespecified operational procedures. Such a committee also might be created if there were safety concerns about the drug or the treatment approach. If a DMC is used, a detailed charter with the composition of the committee members, conflicts of interest, decision

[21] All-cause mortality rates depend on the severity of disease and underlying patient characteristics. We evaluated all-cause mortality rates observed in recently conducted clinical trials submitted for review, which varied between 8 percent to 28 percent (see Sorbello, A, S Komo, T Valappil, and S Nambiar, 2010, Registration Trials of Antibacterial Drugs for the Treatment of Nosocomial Pneumonia, Clinical Infectious Diseases, 51 (S1): S36 – S41). The reasons for the large variability in all-cause mortality rates are not entirely clear, but in general the trials that enrolled a greater proportion of patients with VABP or trials that enrolled patients with a greater likelihood of a mortality outcome had all-cause mortality rates of approximately 20 percent or greater.

rules, details on the measures taken to protect operational bias and the integrity of the trial, and the standard operating procedures should be provided for review.[22]

f. Secondary analyses

Sponsors can present secondary analyses on other endpoints of interest. An analysis of patients who initiate rescue antibacterial drug therapy between the treatment groups is a recommended secondary endpoint; imbalances between treatment groups in the proportion of patients who initiate rescue antibacterial drug therapy can be an important consideration for overall efficacy. Sponsors can present secondary analyses on other endpoints of interest that can include but not be limited to the following:

- Evaluation of internal consistency of the results using responses based on patient demographic characteristics, such as age, sex, geographic region, underlying medical conditions, and microbiological etiology

- Time to mortality analysis by treatment group (e.g., Kaplan-Meier method)

g. Statistical analysis plan

Before initiation of any phase 3 trial, sponsors should provide a detailed statistical analysis plan with the protocol for the phase 3 trial.

C. Other Considerations

1. Pharmacokinetic/Pharmacodynamic Considerations

The PK/PD of the drug should be thoroughly evaluated. The results from nonclinical PK/PD assessments should be integrated with the findings from phase 1 PK studies to help identify the appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials.

Consideration should be given to obtaining sparse samples from all patients in phase 2 and phase 3 clinical trials to allow for the estimation of drug exposure in each patient. Collection of PK data in phase 2 clinical trials can be used to explore the exposure-response relationship and to confirm that the proper dosing regimen is selected for further evaluation in phase 3. Collection of PK data in phase 3 clinical trials may help to resolve any potential questions regarding efficacy or safety that arise from the clinical trials.

A retrospective exposure-response analysis based on the population PK model might help to assess the relationship between PK/PD indices and observed clinical and microbiologic outcomes. The relationship between drug exposure and clinically relevant adverse events should also be explored to identify potential risks with different dosing regimens (if applicable) and specific patient populations.

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[22] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

2. Labeling Considerations

The labeled indication should reflect the patient population enrolled in the clinical trials. Two successful trials in patients with VABP would support a labeled indication for treatment of both HABP and VABP. One successful trial in HABP patients and one successful trial in VABP patients would support a labeled indication for treatment of both HABP and VABP. Two successful trials in patients with HABP would support a labeled indication for treatment of HABP.

3. Risk-Benefit Considerations

Risk-benefit considerations depend on the population being studied and the safety profile of the drug being investigated. For example, in areas where a drug demonstrates meaningful therapeutic advantage in patients with unmet needs, a greater degree of risk or uncertainty may be offset by the benefit provided in an overall evaluation of risk and benefit.

APPENDIX A: JUSTIFICATION FOR A NONINFERIORITY MARGIN FOR CLINICAL TRIALS EVALUATING ANTIBACTERIAL DRUGS FOR TREATMENT OF HABP/VABP

A clinical trial design using an active-comparator antibacterial drug is recommended for the evaluation of a test antibacterial drug in clinical trials of HABP/VABP. One type of active-controlled trial is the noninferiority trial. The principles of the noninferiority clinical trial design and defining an appropriate noninferiority margin are described in ICH E10 and guidances for industry.[23] The finding of noninferiority demonstrates that the test drug is not worse than the active-comparator drug by a specified acceptable amount, or noninferiority margin. An important first step in the justification of a noninferiority margin is an understanding of the treatment effect of the active-comparator drug that can be reliably distinguished from placebo (M1). This information is usually derived from previously conducted placebo-controlled trials; however, no placebo-controlled trials have been conducted that enrolled patients with HABP/VABP. Therefore, this appendix describes an approach to provide historical evidence of sensitivity to drug effect and support M1 by using studies identified from a literature review that were not placebo-controlled studies. Sponsors should use the information contained in this appendix when considering the justification for a noninferiority margin in active-controlled trials for treatment of HABP/VABP designed for noninferiority.

Historical Evidence of Sensitivity to Drug Effects

Placebo-controlled trials provide the most direct estimate of an active-comparator drug's treatment effect. In the absence of placebo-controlled trials, as in the case of HABP/VABP, additional data from other studies including observational studies or active-controlled trials can be used to evaluate a comparator drug's treatment effect. Another aspect that pertains to historical evidence is the constancy assumption. That is, are there reliable data that a comparator drug's treatment effect would not differ between studies conducted today and studies conducted previously?

A literature search was performed to identify published studies with keywords and synonyms related to HABP/VABP. Examples of keywords used include *nosocomial pneumonia* and *ventilator-associated pneumonia*. In addition, because of multidrug resistance and use of an antibacterial therapy to which a bacterial pathogen is resistant might be considered similar to a *placebo* effect, keywords related to inappropriate antibacterial therapy in hospitalized patients with pneumonia were used in a search. Examples of keywords used include *inadequate therapy* and *delayed initiation*. Finally, publications describing the effects of antibacterial drugs that are recommended in treatment guidelines for HABP/VABP were reviewed.

A total of 36 relevant publications were identified that provided data on all-cause mortality and clinical response criteria in patients with HABP/VABP. However, 16 publications did not

[23] See the guidance for industry *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval* and the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. ICH guidances can also be found on this Web site.

distinguish the mortality or clinical outcome data among the subgroups of patients in the ITT population or in different populations (i.e., inappropriate versus appropriate antibacterial therapy). Twenty publications were identified as having sufficient data for inclusion in the analysis to evaluate the HESDE. The entry criteria for each study included patients with a pulmonary infiltrate on chest radiography in addition to fever, leukocytosis, and purulent respiratory tract secretions. A total of 14 publications were observational studies among patients that received either appropriate antibacterial treatment or inadequate treatment (e.g., patients receiving antibacterial therapies that were later found to be resistant to the bacterial pathogen). Six studies were randomized, prospective, active-controlled efficacy studies for the evaluation of drugs for treatment of HABP or VABP.

HESDE was not based on the within-study differences reported between appropriate compared to inadequate, delayed, or inappropriate initial antibacterial therapy in the historical observational studies for two reasons. First, the dosing or duration of appropriate antibacterial treatment regimens was not specified in any of the reports, so that we could not confirm that treatment regimens designated as adequate therapy actually represented the best antibacterial treatment available for HABP and VABP at the time the studies were conducted. Second, there were substantial within-study disparities with respect to age, severity of illness (e.g., APACHE II scores), and baseline pathogens, which are important measured baseline characteristics that can potentially affect the risk for death independent of the adequacy of the administered antibacterial drugs. Additionally, because the studies were nonrandomized, we were concerned about confounding caused by an unequal distribution of unmeasured prognostic factors associated with mortality across treatment arms within each study that can also affect the risk for death independent of the adequacy of the administered antibacterial drugs. Thus, it was necessary to base HESDE on cross-study comparisons. When conducting cross-study comparisons, it is critical that the active-comparator and inadequate, delayed, or inappropriate treatment groups be similar in terms of baseline demographics, severity of illness, and any other factors that can affect mortality. For this reason, a subset of only seven of the studies was used to estimate the HEDSE.

Studies in Patients Who Received Inadequate, Delayed, or Inappropriate Treatment for HABP/VABP

The 14 studies that reported outcomes among patients that received inadequate treatment were reviewed for an estimate of all-cause mortality in the inadequate, delayed, or inappropriate treatment groups.[24] Clinical responses were not provided in a standardized or consistent manner in many of these studies, and therefore clinical responses cannot be *pooled* into an estimate of the treatment effect. Because all-cause mortality was identified from each of these studies, an estimate of all-cause mortality in inadequate, delayed, or inappropriately treated patients can be determined. Two retrospective studies described a small number of patients left untreated, but did not provide demographic characteristics or clear explanations for why these patients were left untreated. The other 12 studies were used in the estimation of an all-cause mortality rate in inadequate, delayed, or inappropriately treated patients. The studies showed variations in population sizes from 65 to 430 patients. Demographic characteristics differed among the studies, with mean APACHE II scores varying from 17.2 to 26.2 and mean ages varying from 42

[24] See Appendix B for a listing of the 14 studies.

years to 67 years. An exact time period for the reporting of all-cause mortality was not specified in the studies; seven studies did not specify a time period at all and the other studies reported all-cause mortality during hospitalization or included some period of time after discharge from an intensive care unit (ICU) setting or from a hospital. The amount of time spent in an ICU or hospital can vary widely among different patients, so it was not possible to identify a specific time point after initiation of treatment in an estimate of all-cause mortality.

The point estimate of all-cause mortality among inadequate, delayed, or inappropriately treated patients in the studies varied from 35 percent to 92 percent. Table 1 depicts the results of the 14 studies.

Table 1. Nonrandomized Clinical Studies Involving Inadequate, Delayed, or Inappropriate Therapies in Hospitalized Patients With Nosocomial Pneumonia Used to Estimate the All-Cause Mortality Rate

Study/First Author	Number of Patients With Nosocomial Pneumonia (% VAP)	Inappropriate Treatment Group All-Cause Mortality n/N (%)	Appropriate Treatment Group All-Cause Mortality n/N (%)	Reporting Time Period for All-Cause Mortality
Alvarez-Lerma	430 (not reported)	51/146 (35%)	92/284 (32%)	72 hours after ICU discharge
Celis	118 (71%)	11/12 (92%)	33/108 (31%)	Not reported
Iregui	107 (100%)	23/33 (70%)	21/74 (28%)	During hospitalization
Kollef	130 (100%)	31/51 (61%)	17/51 (33%)	Not reported
Leone	115 (100%)	7/15 (47%)	20/100 (20%)	Not reported
Leroy	132 (100%)	16/26 (62%)	42/106 (40%)	Deaths at ICU discharge
Luna 2006	76 (100%)	33/52 (64%)	7/24 (29%)	28-days after VAP onset
Luna 2003	63 (100%)	9/13 (69%)	23/50 (46%)	28-days during hospitalization
Luna 1997	65 (100%)	40/49 (82%)	6/16 (38%)	During hospitalization
Rello	121 (100%)	5/11 (45%)	34/110 (31%)	Not reported
Smith	85 (not reported)	5/8 (62%)	37/77 (48%)	Not reported

continued

Table 1, continued

Study/First Author	Number of Patients With Nosocomial Pneumonia (% VAP)	Inappropriate Treatment Group All-Cause Mortality n/N (%)	Appropriate Treatment Group All-Cause Mortality n/N (%)	Reporting Time Period for All-Cause Mortality
Stevens	75 (not reported)	20/34 (59%)	33/41 (80%)	Not reported
Teixeira	151 (100%)	35/69 (51%)	24/82 (29%)	28-days after VAP onset
Torres	78 (100%)	14/27 (52%)	12/51 (23%)	Not reported
DerSimonian and Laird random effects meta-analysis for the all-cause mortality rate from all studies in inappropriate, delayed, or inadequately treated patients			60% (95% CI 49%, 69%)	
Kollef and **Luna 2006:** DerSimonian and Laird random effects meta-analysis for the all-cause mortality rate in inappropriate, delayed, or inadequately treated patients			62% (95% CI 52%, 71%)	

The data from all 14 studies were used in a DerSimonian and Laird random effects meta-analysis that yielded an estimate of all-cause mortality of 60 percent (95 percent CI 49 percent, 69 percent) for inadequate, delayed, or inappropriately treated patients.[25] It was noted that most of the studies were single-center or had missing demographic characteristics that provided limitations on the ability to interpret the all-cause mortality data. In general, for each study all-cause mortality was lower in the patients that received appropriate therapy in comparison to the patients that received inadequate, delayed, or inappropriate therapies. Two studies were identified where patients had similar demographic characteristics and similar clinical severity scores to three of the studies identified among the active-controlled treatment studies.[26] An analysis of all-cause mortality based on patients receiving inappropriate therapies for nosocomial pneumonia or ventilator-associated pneumonia in these two studies was deemed most appropriate. A DerSimonian and Laird random effects meta-analysis of all-cause mortality in these two studies yielded an **estimate of all-cause mortality for inadequate, delayed, or inappropriate therapy in HABP/VABP of 62 percent (95 percent CI 52 percent, 71 percent)**.

[25] DerSimonian, R and N Laird, 1986, Meta-Analysis in Clinical Trials, Controlled Clin Trials, 7:177-188.

[26] Kollef, MH and S Ward, 1998, Chest, 113:412-420; and Luna, CM, P Aruj, MS Neiderman, et al., 2006, Eur Respir J, 27:158-164.

Controlled Studies of HABP/VABP

The mortality rate for an active-comparator antibacterial drug was evaluated by examining studies reporting mortality among patients with HABP/VABP treated with antibacterial drugs recommended in current guidelines for treatment by the American Thoracic Society/Infectious Disease Society of America. Eight studies were found that evaluated the antibacterial drugs considered appropriate for initial treatment for HABP/VABP: piperacillin/tazobactam, imipenem, ceftazidime, ciprofloxacin, levofloxacin, vancomycin, and linezolid.[27] The demographic characteristics including age, mean APACHE II scores, and duration of antibacterial treatment showed some variability among the eight studies. Although clinical responses were reported in these studies, only all-cause mortality was evaluated as a treatment effect because the reporting of clinical response endpoints was not standardized across the studies. Three studies were open-label and five studies were double-blind. Several of the studies included an aminoglycoside antibiotic for additional Gram-negative bacterial coverage. A limitation of these studies is the concomitant administration of an aminoglycoside antibiotic; the actual treatment effect of an individual antibacterial drug may be overestimated.

Among the groups of patients treated with these different antibacterial drugs, the point estimates of the reported mortality rates were between 8 percent and 31 percent, as depicted in Table 2.

Table 2. Prospective, Controlled Clinical Trials in Nosocomial Pneumonia Used to Estimate the Treatment Effect of a Control Antibacterial Drug

Study/First Author	Number of Patients With Nosocomial Pneumonia (% VAP)	Treatment Group* 1 All-Cause Mortality n/N (%)	Treatment Group* 2 All-Cause Mortality n/N (%)	Reporting Time Period for All-Cause Mortality
Alvarez-Lerma	124 (85.5%)	P/T/A 27/88 (31%)	Cef/A 8/36 (22%)	Not reported
Brun-Buisson	197 (64.5%)	P/T/A 18/98 (18%)	Cef/A 22/99 (22%)	28-days post-randomization
Fink	402 (75.6%)	Imi 38/200 (19%)	Cip 43/202 (21%)	30 days after completion of therapy
Joshi	437 (69.1%)	P/T/To 23/222 (10%)	Imi/To 17/215 (8%)	Not reported
Schmitt	217 (23.5%)	P/T 17/107 (16%)	Imi 11/110 (10%)	Not reported
West	438 (10.7%)	Imi/Cip 32/218 (15%)	Lev/Lev PO 38/220 (17%)	28-32 days after completion of therapy

continued

[27] See Appendix B for the studies that evaluate the antibacterial drugs considered appropriate for initial treatment.

Table 2, continued

Study/First Author	Number of Patients With Nosocomial Pneumonia (% VAP)	Treatment Group* 1 All-Cause Mortality n/N (%)	Treatment Group* 2 All-Cause Mortality n/N (%)	Reporting Time Period for All-Cause Mortality
Rubinstein	396 (57.3%)	Lin/Az 36/203 (18%)	Van/Az 49/193 (25%)	12-28 days after completion of therapy
Wunderink	623 (50.6%)	Lin/Az 64/321 (20%)	Van/Az 61/302 (20%)	15-21 days after completion of therapy
Alvarez-Lerma, **Fink**, **West, Rubinstein, and Wunderink:** DerSimonian and Laird random effects meta-analysis for a rate of all-cause mortality in an active control			20% (95% CI 18%, 23%)	

* The data in the table are presented by the treatment groups (1 and 2) for these active-controlled studies; A = amikacin; Cef = ceftazidime; Cip = ciprofloxacin; Imi = imipenam/cilastatin; Lev = levofloxacin; P/T = piperacillin/tazobactam; To = tobramycin; Lin = linezolid; Az = Aztreonam; Van = vancomycin.

As noted above, there was some variability in demographic characteristics among the studies. Five studies[28] appeared to have similar patient demographic characteristics and clinical disease severity scores to the two studies[29] identified among the inadequately, delayed, or inappropriately treated groups. These studies were considered to be the most appropriate to use in an estimate of an active-controlled all-cause mortality rate, following treatment with piperacillin/tazobactam, imipenem/cilastatin, ceftazidime, ciprofloxacin, or levofloxacin. A DerSimonian and Laird random effects meta-analysis of all-cause mortality in these five studies yielded an **estimate of all-cause mortality for an active-comparator antibacterial drug of 20 percent (95 percent CI 18 percent, 23 percent)**.

Summary and Determination of Noninferiority Margin for HABP/VABP

The available data from seven studies with similar patient populations allow an estimate of the effect of inadequate,[30] delayed, or inappropriate therapies and an estimate of the effect of appropriate antibacterial active-controlled drugs. The difference between the two estimates can

[28] Alvarez-Lerma, F, J Insausti-Ordenana, R Jorda-Marcos, et al., 2001, Intensive Care Med, 27:493-502; Fink, MP, DR Snydman, MS Neiderman, et al., 1994, Antimicrob Agents Chemother, 38:547-557; West, M, BR Boulanger, C Fogarty, et al., 2003, Clin Ther, 25:485-506; Rubinstein, E, SK Cammarata, TH Oliphant, et al., 2001, Clin Infect Dis, 32:402-412; Wunderink, RG, SK Cammarata, TH Oliphant, et al.,2003, Clin Ther, 25:980-992.

[29] Kollef, MH and S Ward, 1998, Chest, 113:412-420; Luna, CM, P Aruj, MS Neiderman, et al., 2006, Eur Respir J, 27:158-164.

[30] Kollef, MH and S Ward, 1998, Chest, 113:412-420; Luna, CM, P Aruj, MS Neiderman, et al., 2006, Eur Respir J, 27:158-164; Alvarez-Lerma, F, J Insausti-Ordenana, R Jorda-Marcos, et al., 2001, Intensive Care Med, 27:493-502; Fink, MP, DR Snydman, MS Neiderman, et al., 1994, Antimicrob Agents Chemother, 38:547-557; West, M, BR Boulanger, C Fogarty, et al., 2003, Clin Ther, 25:485-506; Rubinstein, E, SK Cammarata, TH Oliphant, et al., 2001, Clin Infect Dis, 32:402-412; Wunderink, RG, SK Cammarata, TH Oliphant, et al.,2003, Clin Ther, 25:980-992.

be used to help understand an active-controlled drug's treatment effect over inadequate, delayed, or inappropriate therapies (M1). The all-cause mortality rate was 62 percent (95 percent CI 52 percent, 71 percent) for patients treated with inadequate, delayed, or inappropriate therapies and the all-cause mortality rate was 20 percent (95 percent CI 18 percent, 23 percent) for patients treated with an active-controlled drug. Although the DerSimonian and Laird model accounts for some of the variability of the data, it is still appropriate to remain conservative when considering an estimate of M1. Therefore, the lower bound of the 95 percent CI for the treatment effect of inadequate, delayed, or inappropriate therapies minus the upper bound of the 95 percent CI for an estimate of the treatment effect of an active-comparator antibacterial drug results in an estimate of the treatment effect of an antibacterial drug over inadequate, delayed, or inappropriate therapies of approximately 29 percent (52 percent *minus* 23 percent). This estimate of M1 from HESDE has several limitations as described below:

- There are no placebo-controlled studies in the historical literature

- The HESDE for treatment of HABP/VABP was derived from only seven studies: two studies for the estimate of the effect of inadequate, delayed, or inappropriate therapies and five studies for the estimate of the effect of appropriate therapy

- Some of the studies were open-label comparisons or observational studies leading to the potential for bias; only three studies incorporated double-blinded randomization

- There was variability in baseline patient demographics and disease severity across the studies

- The studies assessed mortality at different time points or did not state when mortality was assessed

- The cross-study comparisons to arrive at estimates of all-cause mortality rates create uncertainties: the all-cause mortality rates were higher in the appropriately treated groups for the studies that were used in the estimate of the treatment effect of inadequate, delayed, or inappropriate therapies (see Table 1) in comparison to the all-cause mortality rates in the active-controlled studies that were used in the estimate of the treatment effect of appropriate therapy (see Table 2)

- Technological advances over time in the management of patients in intensive care units may lead to variability in the estimates of all-cause mortality rates in the historical studies.

One of the strategies employed in choosing the margin M1 for the noninferiority study design is that of *discounting* or reducing the magnitude of the margin size that is used in the noninferiority study from what is calculated from the analysis of HESDE. Such discounting is done to account for the uncertainties in the assumptions that need to be made in estimating, based on past performance, the effect of the active control. This concept of discounting focuses on M1 determination and is distinct from a clinical judgment that the effect that can be lost on clinical grounds should be some fraction of M1 (i.e., M2). Given the limitations and uncertainties listed above, the treatment effect should be further discounted to determine M1. To account for these limitations and uncertainties, the treatment effect of 29 percent was discounted by an additional 30 percent to arrive at an M1 of 20 percent. **Thus, a conservative and reliable estimate of the treatment effect on all-cause mortality of an antibacterial drug against placebo (M1) in the treatment of HABP/VABP is approximately 20 percent.**

The noninferiority clinical trial should demonstrate similarity to the historical studies used to estimate the treatment effect (the constancy assumption) based on a patient population with approximately 20 percent all-cause mortality rate in the active treatment groups. As such, the active-controlled drug should have an all-cause mortality rate of approximately 20 percent (see Table 2) to maintain the constancy assumption in noninferiority clinical trials. If the active control all-cause mortality rate is less than approximately 20 percent, an odds ratio can be considered as a measure for assessing treatment effects. However, the constancy assumption may not be valid for an all-cause mortality rate of less than 20 percent in the active-control group. Sponsors considering using the odds ratio as a measure for assessing treatment effects should discuss their plans with the FDA during clinical development.

In addition to the scientific and statistical justifications, the prespecified amount by which a test antibacterial drug is allowed to be inferior should also be subject to clinical judgment. A large proportion of M1 should be preserved to be clinically acceptable with respect to the efficacy of a test drug on the endpoint of all-cause mortality. **A noninferiority margin of 10 percent is recommended to preserve the treatment effect of antibacterial drug therapy in a noninferiority clinical trial that enrolls patients with HABP or VABP. All-cause mortality within 28 days after randomization in the active-control group should be approximately 20 percent or greater to preserve the constancy assumption. All-cause mortality should be the primary endpoint at 28 days after randomization.**

APPENDIX B: LISTINGS OF LITERATURE REVIEWED FOR HISTORICAL EVIDENCE

The 14 studies reviewed for an estimate of the effect of inadequate, delayed, or inappropriate treatment for HABP/VABP (listed in alphabetical order):

- Alvarez-Lerma, F and the ICU-Acquired Pneumonia Study Group, 1996, Modification of Empiric Antibiotic Treatment in Patients With Pneumonia Acquired in the Intensive Care Unit, Intensive Care Med, 22:387-394.

- Celis, R, A Torres, JM Getell, et al., 1988, Nosocomial Pneumonia: A Multivariate Analysis of Risk and Prognosis, Chest, 93(2):318-324.

- Iregui, M, S Ward, G Sherman, VJ Fraser, and MH Kollef, 2002, Clinical Importance of Delays in the Initiation of Appropriate Antibiotic Treatment of Ventilator-Associated Pneumonia, Chest, 122:262-268.

- Kollef, MH and S Ward, 1998, The Influence of Mini-BAL Cultures on Patient Outcomes: Implications for the Antibiotic Management of Ventilator-Associated Pneumonia, Chest, 113:412-420.

- Leone, M, F Carcin, J Bouvenot, et al., 2007, Ventilator-Associated Pneumonia: Breaking the Vicious Circle of Antibiotic Overuse, Crit Care Med, 35:379-385.

- Leroy, O, A Meybeck, T d'Escrivan, et al., 2003, Impact of Adequacy of Initial Antimicrobial Therapy on the Prognosis of Patients With Ventilator-Associated Pneumonia, Intensive Care Med, 29:2170-2173.

- Luna, CM, P Aruj, MS Neiderman, et al., 2006, Appropriateness and Delay to Initiate Therapy in Ventilator-Associated Pneumonia, Eur Respir J, 27:158-164.

- Luna, CM, D Blanzaco, MS Neiderman, et al., 2003, Resolution of Ventilator-Associated Pneumonia: Prospective Evaluation of the Clinical Pulmonary Infection Scores as an Early Clinical Predictor of Outcome, Crit Care Med, 31:676-682.

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- Rello, J, L Vidaur, A Sandiumenge, et al., 2004, De-Escalation Therapy in Ventilator-Associated Pneumonia, Crit Care Med, 32:2183-2190.

- Smith, IM, MC Champion, EC Hazard, L Lowry, PE Leaverton, 1970, Single and Combined Antibiotics in the Treatment of Pseudomonas Aeruginosa Infections, In: Progress in Antimicrobial and Anticancer Chemotherapy: Proceedings of the 6th International Congress of Chemotherapy, Volume 1, Baltimore, MD: University Park Press, 718-724.

- Stevens, RM, D Teres, J Skillman, and DS Feingold, 1974, Pneumonia in an Intensive Care Unit: A 30 Month Experience, Arch Intern Med, 134:106-111.

- Teixeira, PJA, R Seligman, FT Hertz, DB Cruz, and JMG Fachel, 2007, Inadequate Treatment of Ventilator-Associated Pneumonia: Risk Factors and Impact on Outcomes, J Hosp Infect, 65:361-367.

- Torres, A, R Aznar, JM Gatell, et al., 1990, Incidence, Risk, and Prognosis Factors of Nosocomial Pneumonia in Mechanically Ventilated Patients, Am Rev Respir Dis, 142:523-528.

The eight studies that evaluated appropriate antibacterial drugs for initial treatment of HABP/VABP (listed in alphabetical order):

- Alvarez-Lerma, F, J Insausti-Ordenana, R Jorda-Marcos, et al., 2001, Efficacy and Tolerability of Piperacillin/Tazobactam Versus Ceftazidime in Association With Amikacin for Treatment of Nosocomial Pneumonia in Intensive Care Patients: A Prospective, Randomized, Multicenter Trial, Intensive Care Med, 27:493-502.

- Brun-Buisson, C, JP Sollet, S Briere, et al., 1998, Treatment of Ventilator-Associated Pneumonia With Piperacillin-Tazobactam/Amikacin Versus Ceftazidime/Amikacin: A Multicenter, Randomized, Controlled Trial, Clin Infec Dis, 26:346-54.

- Fink, MP, DR Snydman, MS Neiderman, et al., 1994, Treatment of Severe Pneumonia in Hospitalized Patients: Results of a Multicenter, Randomized, Double-Blind Trial Comparing Intravenous Ciprofloxacin With Imipenem/Cilastatin, Antimicrob Agents Chemother, 38:547-557.

- Joshi, M, M Metzler, M McCarthy, et al., 2006, Comparison of Piperacillin/Tazobactam and Imipenem/Cilastatin, Both in Combination With Tobramycin, Administered Every Six Hours for Treatment of Nosocomial Pneumonia, Respir Med, 100:1554-1565.

- Rubinstein, E, SK Cammarata, TH Oliphant, et al., 2001, Linezolid (PNU-100766) Versus Vancomycin in the Treatment of Hospitalized Patients With Nosocomial Pneumonia: A Randomized, Double-Blind, Multicenter Study, Clin Infect Dis, 32:402-412.

- Schmitt, DV, E Leitner, T Welte, H Lode, 2006, Piperacillin/Tazobactam Versus Imipenem/Cilastatin in the Treatment of Nosocomial Pneumonia — A Double-Blind, Prospective, Multicenter Study, Infection, 34:127-134.

- West, M, BR Boulanger, C Fogarty, et al., 2003, Levofloxacin Compared With Imipenem/Cilastatin Followed By Ciprofloxacin in Adult Patients With Nosocomial Pneumonia: A Multicenter, Prospective, Randomized, Open-Label Study, Clin Ther 2003, 25:485-506.

- Wunderink, RG, SK Cammarata, TH Oliphant, et al., 2003, Continuation of a Randomized, Double-Blind, Multicenter Study of Linezolid Versus Vancomycin in the Treatment of Patients With Nosocomial Pneumonia, Clin Ther, 25:980-992.